UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/896,053	07/17/97	JANSSENS S	0609.4280001

HM12/0624

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EXAMINER	
BECKERLEG, A	
ART UNIT	**PAPER NUMBER**
1632	11

DATE MAILED: 06/24/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/896,053	Applicant(s) Janssens
	Examiner Anne Marie S. Beckerleg	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Mar 30, 1999*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-21* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The applicant's amendment received 3/30/99 has been entered. Claims 3,9, and 17 have been amended and new claim 21 has been added. Claims 1-21 are pending in the instant application.

The objection to the oath or declaration is maintained. The examiner acknowledges the applicant's intent to correct the defects in the declaration until such time that allowable subject matter has been indicated.

The rejection of claims 1-20 and newly added claim 21 under 35 U.S.C. 112, first paragraph, is maintained in part. The applicant's arguments have been considered but have not been found persuasive in overcoming the instant grounds of rejection detailed in the office action of 9/28/98. The applicant's arguments are addressed in detail below.

As stated in the previous office action, the specification, while being enabling for a method of inducing vasodilation in a mammal comprising: introducing into the lungs of a mammalian patient in need of pulmonary vasodilation an aerosolized adenoviral vector comprising a wild type nitric oxide synthase gene operably linked to the CMV promoter, wherein the introduction of said gene into the lungs of said patient results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index, and a method of treating hypoxic pulmonary hypertension in rats comprising introducing into the lungs of a rat in need of pulmonary vasodilation an aerosolized adenoviral comprising a wild type nitric oxide synthase gene operably linked to the CMV promoter, wherein the introduction of said gene into the lungs of said rat

results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index, does not reasonably provide enablement for a method of treating any and all forms of primary or secondary hypertension in all mammals comprising introducing by any route of delivery, any vector encoding any nitric oxide synthase gene under the control of any promoter.

The applicant's arguments have been found persuasive concerning the enablement in the specification for other wild type forms of nitric oxide synthase, such as inducible NOS and neuronal NOS. However, the applicant's arguments do not overcome the lack of enablement in the specification for addition/deletion mutants of any NOS gene. The applicant argues that the specification teaches regions of shared homology between the different NOS isoforms and provides guidance for substituting, deleting, or adding nucleotides to the wild type NOS gene such that the mutated gene retains the wild type function of NOS. Further, the applicant argues that Huang et al. provides structure-function information for iNOS, nNOS, and ceNOS that would presumably guide the skilled artisan in making mutations to these genes. Huang et al. teaches the effects of knocking out the expression of iNOS, nNOS, and ceNOS in mice. Huang et al. does not teach or suggest making mutations in NOS genes wherein the NOS gene product retains wild type activity, or identify amino acid residues that can be mutated without significantly altering NOS bioactivity. Thus, Huang et al. does not overcome the lack of guidance in the specification for making bioactive addition or deletion mutants for any NOS isoform. As to the guidance provided by the specification, the pages and passages indicated by the applicant, pages 12-14, and particularly page 11, lines 19-23, disclose preferred types of amino acid substitutions

for single residues. However, the specification on page 13 also teaches that much more substantial amino acid substitutions can be made which may alter the structure, charge, and hydrophobicity of the polypeptide backbone. It was well known at the time of filing that these types of major changes, even when they occur outside of the established active sites of a protein or enzyme, can have a profound effect on the activity of the modified protein. In the absence of specific guidance for structural, charge, and hydrophobicity modifications to the NOS proteins, the skilled artisan would not have had a reasonable expectation of success in maintaining the wild type NOS activity following additions, deletions, or substitutions that affect the structure of the polypeptide backbone, the charge, and the hydrophobicity of an NOS gene.

The applicant's arguments are not persuasive in overcoming the lack of enablement in the specification for the use of any and all vectors/promoters which encode a wild type NOS, and any and all routes of delivery of said vectors to a mammal wherein the expression of NOS results in vasodilation or has any therapeutic effect on pulmonary hypertension. The applicant correctly states that the burden of establishing the non-enablement of the specification rests on the examiner, and that, "[w]here... the examiner is concerned about the breadth of a generic term, the recitation of the term must be taken as an assertion that all of the species included within the generic term would, as a class, be operative to produce the asserted affect" (applicant's amendment of 3/30/99, page 6, paragraph 2). The applicant also cites *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971), which states, "[t]he only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion". In response to

these statements, it is noted that in making a scope of enablement rejection, the examiner has appropriately identified the enabled embodiments of the broad generic claims in the instant application, and has provided arguments supported by teachings in the prior art which question the operativeness of any and all species which are included by the generic terms "vector", "expression control elements", and "introducing" recited by the applicant in the specification and the claims.

The applicant argues that the examiner has not provided specific reasons why any and all vectors and delivery systems are not enabled by the specification. The examiner notes that specific reasons for finding a lack of enablement for the delivery of any vector which encodes NOS can be found on pages 4-5 of the previous office action. In summary, the reasons of record identify the following art-recognized problems associated with the vector systems available at the time of filing: the inability of retroviral vectors to infect non-dividing cells such as those found in the lung, the lack of stable transgene expression due to immunological recognition of virally infected cells, the lack of sufficient levels of gene expression due to problems associated with the use of any and all promoters such as inducible promoters and cell-specific promoters, and the unpredictability of achieving targeted gene delivery where the vector is introduced at a location other than the target location (Verma et al., Orkin et al.).

The specification argues that Verma et al. does not support the unpredictability of gene therapy using any and all vectors and promoters as indicated by the examiner. In particular, the applicant argues that while Verma does teach that one of the major limitations to *in vivo* delivery

and expression of genes by retroviruses is their inability to infect dividing cells such as those found in the lung, Verma also teaches that retroviruses can infect normally non-dividing cells that have been removed from the animal and grown *in vitro* and that these transduced cells can be re-introduced back into the animal (Verma et al., page 240). However, the applicant's claims are not limited to *ex vivo* gene therapy, and clearly read on the direct *in vivo* administration of retroviral and other vectors. In addition, while the specification makes a single statement on page 16 that macrophages can be transduced *in vitro* and reintroduced into the patient, the specification does not provide guidance as to other cell types that can be used, or the dosage or routes of re-delivery for the transduced cells back into the animal such that therapeutic levels of NOS would be expressed at the site of hypoxic injury or at an site in need of vasodilation. Further, continuing on page 240, Verma et al. teaches that *ex vivo* gene therapy also faces formidable challenges, such as efficiency of transplantation of the infected cells, transiency of transgene expression, and the inadequacy of current model systems based on inbred animals (Verma et al., page 240, column 3). Finally, the applicant's suggestion that Verma highlights the high level of sophistication in gene therapy that existed in the mid-1990's by teaching the existence of over 200 gene therapy trials, ignores the article's analysis of the trial data which concludes that the disappointing outcome of those trials can be attributed to inefficient gene-delivery systems (Verma et al., page 242, column 2, lines 3-5). The applicant's conclusion that the teachings of Verma taken as a whole support the predictability of gene therapy appears to be based on a single prophetic sentence at the conclusion of the article, ".. in the not too distant future, gene therapy will become as routine a practice as

heart transplants are today" (Verma et al., page 242, last sentence). While the final sentence of the article expresses the authors hope that the problems associated with gene therapy will be surmounted in the not too distant future, the body of the paper clearly defines and discusses in detail the major obstacles to gene therapy at the time of filing using the currently available vector systems, and teaches the unpredictability of using these vectors for gene therapy based on the disappointing outcomes of the current clinical trials.

In a footnote to page 8 of the applicant's amendment, the applicant cites Scott-Taylor et al. and Halbert et al. as examples of cases where adenoviral vectors have been used to pre-condition cells for retroviral infection, and where retroviral vectors have been successfully used to infect lung cells *in vivo* respectively. Scott-Taylor et al. was published after the filing of the instant application, and teaches that cells which do not express retroviral receptors can be made susceptible to retroviral infection by pre-treatment with an adenovirus which expresses a retroviral receptor. The recombinant adenoviral vector taught by Scott-Taylor is not disclosed in the instant specification. Further, the specification fails to provide a nexus between the instant invention, which utilizes the administration of a single vector, and the teachings of Scott-Taylor et al., which uses the combined administration of an adenoviral vector which expresses a retroviral receptor and a retrovirus. In the case of Halbert et al., stimulation of wound healing by brushing the trachea prior to administration of a retrovirus resulted in transient expression of the retrovirally encoded transgene in cells in the wounded area of the trachea. Halbert et al., however, clearly teaches that only cells stimulated to divide by abrasion were infected and that transduction

efficiency and transgene expression were very low. Retroviral administration to unabraded tissue resulted in no detectable gene expression. The specification does not teach or suggest abrading tissue in the lung or trachea in order to stimulate cell division prior to the administration of a vector, or provide a nexus between the abrasion technique taught by Halbert et al. and the instant methods of administration taught by the specification. Thus, Halbert et al. clearly demonstrates the unpredictability of achieving therapeutic levels of transgene expression by direct *in vivo* administration of a retrovirus to the lung or trachea in the absence of brush abrasion. Further, Halbert et al. supports the teachings of Verma et al. by teaching that present efforts in gene therapy to airway epithelia using adenoviral vectors suffers from major problems with immune responses and transient transgene expression (Halbert et al., page 1879, column 2, paragraph 3). Therefore, due to the lack of guidance provided by the specification which would create a nexus between the specialized techniques and vectors taught by Halbert et al. and Scott-Taylor et al., the skilled artisan would not consider these references as providing enablement for the instant methods of delivering viral vectors to any and all cells in the lung.

The applicant argues that Roullet et al. cannot be relied upon to teach the unpredictability of achieving a therapeutic effect on pulmonary hypertension using a composition comprising a vector encoding NOS and cyclosporin A. The applicant cites Roullet as teaching that, "in many studies in which altered vascular reactivity was demonstrated, there was not documented elevation of blood pressure, thereby bringing into question the relevance of the observed vascular changes to hypertension (caused by cyclosporin A) " (Roullet et al., page 2244, column 2,

parentheses added). Taken in context however, this statement refers to previous studies which did not specifically ask the question of whether cyclosporin A directly or indirectly affects blood pressure. Their own experiments were designed to address this issue in particular. The applicant also states that, "although systemic hypertension has been reproduced in animals given CysA, the data are inconsistent" (applicant's amendment, page 9, citing Roullet et al., page 2246). Again, taken in context, the authors state in the preceding sentence that their own data both significantly and reproducibly demonstrates an increase in systolic blood pressure in response to cyclosporin A, and that the inconsistencies observed int eh previously published literature reflect differences in dose, duration of treatment, and type of vehicle. Thus, these statements further demonstrate the complexities of administering an immunosuppressive agent such as cyclosporin A and highlight the potential effects of dose and carrier agents. Furthermore, the applicant's arguments that the data presented by Roullet et al. concerning the negative effects of cyclosporin A on vasorelaxation is inconclusive since Roullet does not teach the molecular mechanisms of the interaction is irrelevant. Roullet et al. clearly demonstrates that cyclosporin inhibits vasorelaxation, most likely by negatively affecting the NO pathway. In view of these teachings, and in view of the lack of evidence to the contrary provided by the prior art or the specification, the skilled artisan would not have had a reasonable expectation that the combination of a drug that inhibits vasorelaxation and a drug which induces vasorelaxation would have a therapeutic effect on hypertension.

The applicant argues that the specification is enabled for the treatment of pulmonary hypertension using vectors which encode NOS because the rat is an art recognized model of

pulmonary hypertension as supported by Roberts et al. The applicant further argues that the examiner cannot rely on Heath et al. for teaching the unpredictability of using pulmonary vasodilators for treating neointima and plaque formation associated with primary hypertension. The applicant states that Heath et al. does not teach the effects of NOS or NO specifically in regards to pulmonary hypotension, and that the teachings in Heath relating to "vasodilators" does not necessarily read ont eh effects of NO. The applicant bases the latter conclusion on the fact that following the statements cited in the prior office action which read, " [pulmonary vasodilators] are likely to reverse any vasoconstrictive component, it is difficult to conceive what effect they might have on structural changes in the intima..", and that, " [p]ulmonary vasodilators are unlikely to be effective once migration of vascular smooth muscle cells has occurred", Heath et al. discloses an experiment where ligustrazine attenuates right ventricular hypertrophy and muscularization of pulmonary arterioles in hypoxic rats (Heath et al., page 557-558). The applicant argues that since this "vasodilator" can impede smooth muscle growth in rats, it would not be unpredictable that NO or other vasodilators would do the same thing. This argument misses the central point of the Heath article, that rats are a poor animal model for pulmonary hypertension because they do not exhibit migration of smooth muscle cells and that vasodilators would not be predicted to be effective in treating pulmonary hypertension once migration of smooth muscle cells has occurred. The ligustrazine example, which was conducted in rats, does not alter the central teaching of Heath in regards to the unpredictability of using vasodilators to treat primary pulmonary hypertension in mammals such as rabbits or humans, where smooth

muscle migration results in a more complex vascular environment than that observed following induced hypoxia in rats. Roberts et al., cited by the applicant as providing evidence of the efficacy of NO in treating ventricular hypertrophy and smooth muscle growth, is not persuasive in overcoming this deficiency as they also discloses experiments performed in the rat. Further, the applicant is reminded that the examiner has already indicated in the previous office action that the specification is enabling for the treatment of hypoxic pulmonary hypertension in rats. Thus, for the reasons discussed above, the applicant's arguments do not overcome the instant grounds of rejection concerning the lack of enablement in the specification for treating any and all forms of pulmonary hypertension in any and all mammals such as humans.

The rejection of claims 3, 9, and 17 under 35 U.S.C. 112, second paragraph, are withdrawn in view of applicant's amendments to the claims.

The rejection of claim 17 under 35 U.S.C. 103 over Chen et al. in view of Rosenfeld et al. is withdrawn in view of applicant's arguments.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. A.M.S. Beckerleg

June 21, 1998